View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

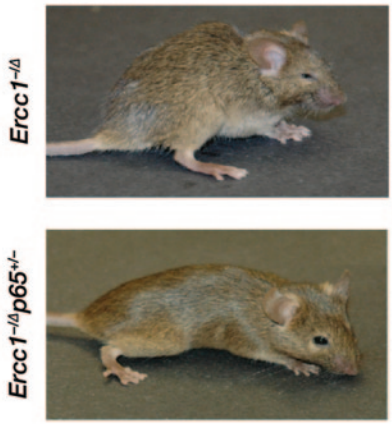


© 2012 International Society of Nephrology

*Kidney International* (2012) **82**, 505–506. doi:10.1038/ki.2012.279

# NF-κB inhibition delays DNA-damage-induced senescence and aging in mice

**Tilstra *et al.***, *J Clin Invest* 2012; **122**: 2601–2612; doi:10.1172/JCI45785




**Representative images of *Ercc1*$^{-/\Delta}$ and *Ercc1*$^{-/\Delta}$p65$^{+/-}$ sex-matched littermates at 15 weeks of age.**

The ability to maintain homeostasis in response to stress declines with age, in part because of the accumulation of the effects of cellular injury, including DNA damage. Though it is well known that DNA damage can induce senescence and other hallmarks of cellular aging, the mechanisms by which DNA damage promotes aging are incompletely understood. Tilstra *et al.* studied an animal model of XFE progeroid syndrome, which is characterized by accelerated aging of virtually all organ systems, including the kidneys, due to the inability to repair endogenous DNA damage. The authors focused on the role of nuclear factor-κB (NF-κB), a transcription factor that is a central regulator of innate immunity, in the pathogenesis of DNA-damage-induced inflammatory injury. Progeroid mice had increased activation of NF-κB in the kidney, liver, pancreas, and muscle compared with wild-type mice. To determine whether NF-κB was necessary for the accelerated aging phenotype, the investigators compared progeroid mice with heterozygous knockout of the NF-κB p65 subunit and progeroid mice with wild-type p65. They found that p65 heterozygous mice had delayed onset of the progeroid phenotype as evidenced by improved appearance (Figure), delayed neurodegeneration and musculoskeletal deterioration, and reduced glomerulosclerosis and renal tubular cast formation. The investigators then studied whether inhibiting NF-κB activation by administration of a peptide inhibitor of IκB kinase (IKK) improved the aging phenotype in progeroid mice. The IKK inhibitor delayed onset of functional decline and histologic organ pathology similarly to heterozygous p65 gene deletion. The investigators then used microarrays to determine the effect of the IKK inhibitor on gene expression in livers of progeroid mice. IKK inhibition reduced activation of typical NF-κB-regulated genes and normalized expression of genes involved in cell-cycle regulation, apoptosis, stress response, and DNA damage. Importantly, the authors then performed *in vitro* and *in vivo* studies that demonstrated that IKK inhibition prevented oxidative stress–induced senescence and protected progeroid mice from oxidative DNA damage.

This important article directly implicates NF-κB in the pathogenesis of aging, suggesting that NF-κB inhibition may be of benefit in the treatment of aging-related disorders.

**Michael Ross**

# Syndecan–syntenin–ALIX regulates the biogenesis of exosomes

**Baietti *et al.***, *Nat Cell Biol* 2012; **14**: 677–685; doi:10.1038/ncb2502

Exosomes are small secreted vesicles derived from the endosomal compartment, where budding of the endosomal membrane generates vesicle-containing endosomes (alternately referred to as late endosomes, multivesicular endosomes, or multivesicular bodies), which release vesicles outside the cell by fusion with the plasma membrane. The structure of exosomes comprises a lipid bilayer membrane, an array of membrane and cytosolic proteins, and selected RNA species. This molecular complexity suggests that exosomes may mediate a variety of physiological and pathological functions. Indeed, a growing number of reports show that these vesicles are crucial in transferring information from one cell to another and play a crucial role in physiological as well as pathological activities. Exosomes are released by most cell types in the extracellular space; moreover, the presence of exosomes *in vivo* in many body fluids, including blood and urine, makes them readily accessible. In fact, human urine contains large numbers of exosomes, released from every renal epithelial cell type facing the urinary space. Thus, their study opens the possibility of obtaining information on the cell of origin in physiological and pathological conditions and of discovering molecular markers of renal dysfunction and structural injury. Despite the identification of a specific endosomal-sorting complex required for transport (ESCRT) machinery that regulates membrane budding, the intracellular processes that regulate exosomal cargo formation and the subsequent abscission of vesicles are not completely understood.

In this study, Baietti and collaborators performed a series of accurate biochemical and functional experiments using native and mutated proteins. They show that the connections between syndecans and syntenin and between syntenin and ALIX (apoptosis-linked gene 2-interacting protein X), a protein relevant to budding and abscission processes, support the biogenesis of exosomes and the segregation of signaling cargos to these specific vesicles. Through syndecan, heparan

sulphate is shown to play a crucial role in this process, as demonstrated by the reduction of exosome release when the heparan sulphate structure is disrupted. These data, therefore, add an additional role for heparan sulphate signaling, which is likely to prove relevant to several disease processes.
**Maria Pia Rastaldi**

## Randomized phase 2b trial of tofacitinib (CP-690,550) in *de novo* kidney transplant patients: efficacy, renal function, and safety at 1 year

**Vincenti *et al.***, *Am J Transplant* advance online publication, 8 June 2012, doi:10.1111/j.1600-6143.2012.04127.x

The search for less nephrotoxic alternatives to calcineurin inhibitors in transplant patients continues. Janus kinase (JAK) is responsible for intracellular signal transduction of multiple cytokines, including interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21, which are essential for the function of T cells, B cells, and natural killer cells. Tofacitinib (CP-690,550) is an oral JAK inhibitor. In a phase 2b study, 331 low- to moderate-risk *de novo* kidney transplant patients (approximately 60% deceased donors) were randomized to a more intensive (MI) or less intensive (LI) regimen of tofacitinib or cyclosporine (CsA). All patients received basiliximab induction, mycophenolic acid, and corticosteroids. The primary end points were incidence of biopsy-proven acute rejection (BPAR) at month 6 and measured glomerular filtration rate (GFR) at month 12. The incidence of BPAR was similar among the groups (11%, 7%, and 9%, respectively), and measured GFRs were higher at month 12 in the MI and LI groups than in the CsA group (65, 65, and 54 ml/min, respectively). Fewer patients in the MI or the LI group developed chronic allograft nephropathy at month 12 compared with the CsA group (25%, 24%, and 48%). However, serious infections developed in 45%, 37%, and 25% of patients in the MI, LI, and CsA groups, respectively. Anemia, neutropenia, and post-transplant lymphoproliferative disorder (PTLD) occurred more frequently in the MI and the LI groups than in the CsA group.

In conclusion, tofacitinib was equivalent to CsA in preventing acute rejection and was associated with improved renal function and less chronic allograft nephropathy. The risk of serious infections and PTLD was much higher. This drug does have the potential to be used in a calcineurin inhibitor-free regimen; however, additional studies are needed to see whether the side effect profile can be improved.
**Jai Radhakrishnan**

## Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis

**Fagundes *et al.***, *J Hepatol* 2012; **57**: 267–273; doi:10.1016/j.jhep.2012.03.015

Acute kidney injury (AKI) is not only more common in patients with advanced hepatic cirrhosis but is also associated with increased mortality. Currently, the most common causes of AKI are prerenal AKI (volume responsive), acute tubular necrosis (volume unresponsive), hepatorenal syndrome (HRS), and drug-induced nephrotoxicity. The cause of AKI has a prognostic impact on patient survival as well as an impact on the utilization and cost of health-care resources. Thus, there is a clinical need to develop a rapid diagnostic test that would help differentiate the cause of AKI, as serum creatinine is typically reduced in advanced cirrhosis because of lower creatine synthesis, protein energy wasting, and bilirubin interference with modified Jaffe colorimetric assays. Fagundes and colleagues measured urinary neutrophil gelatinase associated lipocalin (uNGAL) in 241 patients admitted with advanced cirrhosis. Patients with acute tubular necrosis had markedly higher uNGAL levels (median 417 (interquartile range 239–2242) μg/g creatinine) than those with prerenal AKI (30 (20–59) μg/g creatinine), underlying chronic kidney disease 82 (34–152) μg/g creatinine), and HRS (76 (43–263) μg/g creatinine). Among HRS patients, the highest values were found in HRS precipitated by infections, followed by classical (not associated with active infections) type 1 and type 2 HRS (391 (72–523), 147 (83–263), and 43 (31–74) μg/g creatinine, respectively). Patients with urinary tract infections had higher uNGAL (166 (82–412) μg/g creatinine) than those without urosepsis (42 (19–98) μg/g creatinine). In addition, there were statistically significant differences in uNGAL levels between classical type 1 HRS and acute tubular necrosis, chronic kidney disease, and prerenal AKI (volume responsive AKI).

Further multicenter studies are warranted to explore the sensitivity and specificity of uNGAL in differentiating the causes of AKI in patients with advanced cirrhosis.
**Andrew Davenport**